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10/629,928	07/29/2003	George L. King	10276-060002	1929

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,928	KING, GEORGE L.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *8 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-28-06.

Claims 1-26 are pending in the instant application.

Election/Restrictions

Claims 8 and 9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4-28-06.

Claim Objections

Claim 7 is objected to because of the following informalities: In claim 7, line 2, please replace the ";" following "resistance" with a comma. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-7, 10-12, 14-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of modulating PKCβ and eNOS in a cell or in a subject comprising administration of an inhibitor of PKCβ. The claims are also drawn to a method of diagnosing a risk of hypertension in a subject comprising comparing PKCβ activity in cells or tissues of a subject.

The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the claimed genera, which are broadly drawn to any inhibitor of PKCβ and to any isoform of PKCβ for diagnostic purposes. The genus comprising inhibitors of PKCβ embrace a multitude of agents and chemicals, including but not limited to antibodies, antisense, binding peptides and small molecules, and the disclosure fails to provide a representative number of species for the genus that provide for the function claimed, *i.e.* of inhibiting PKCβ, increasing eNOS and providing treatment effects for insulin related disorders. The disclosure does not clarify the common attributes or provide a representative number of species for adequate description of the encompassed genera that provide for the functions claimed, of inhibiting PKCβ, increasing eNOS and providing treatment effects for insulin related disorders, and for diagnosing hypertension by evaluating any isoform of PKCβ in any cell or tissue. Concise structural features that would distinguish structures within the claimed genera of molecules from those outside of the genera are missing from the disclosure. One of skill in the art would reasonably conclude that the disclosure fails to

provide a representative number of species to describe the genera claimed. Thus, Applicant was not in possession of the broadly claimed genera.

Claims 1-3, 5-7, 10-12, 14-23, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibiting PKCβ and treating diabetes related disorders comprising the administration of LY333531, does not reasonably provide enablement for methods of modulating PKCβ and eNOS in a cell or in a subject, and methods for treating any insulin related disorder, comprising administration of any inhibitor of PKCβ, nor for methods of diagnosing a risk of hypertension in a subject comprising comparing the activity of PKCβ in any cell or tissue of a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of modulating PKCβ and eNOS in a cell or in a subject, and methods for treating any insulin related disorder, comprising administration of any inhibitor of PKCβ. The claims are also drawn to a method of diagnosing a risk of hypertension in a subject comprising comparing the activity of PKCβ in any cell or tissue of a subject to a normal subject.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of treatment in organisms that involves the delivery of molecules including nucleic acid molecules to appropriate cells or tissues in an organism. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo efficacy. (A. Branch, Trends in Biochem. Sci. 23: 45-50, *see* entire text for Branch; S. Crooke, Antisense Research & Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches. Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol. 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide

(S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

See Opalinska (Nature Reviews, Vol. 1, pages 503-514, 2002) for a review of the unpredictabilities associated with the in vivo efficacy of double stranded oligonucleotides for target gene inhibition: "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remain tantalizing, but uncertain." (3rd full paragraph on p. 503). "...it is widely appreciated that the ability of nucleic acid molecules to modify gene expression in vivo is quite variable, ant therefore wanting in terms of reliability." (1st full paragraph on p. 511).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of correlating a risk of hypertension in a population with PKCβ activity. Applicants have not provided any treatment effects for diabetes related conditions comprising a representative number of species of the broad genus comprising inhibitors of PKCβ. The specification teaches an increase in eNOS

expression upon administration of insulin to endothelial cells in vitro. The specification also teaches a lack of increase of eNOS expression upon administration of insulin to vascular stroma isolated from insulin resistant rats. One skilled in the art would not accept on its face the examples given in the specification of the in vitro relationship between eNOS expression and insulin administration of being correlative or representative of the ability to treat any insulin related disorder comprising the administration of any inhibitor of PKCβ in a subject, nor of the ability to diagnose a risk of hypertension in any subject or population by comparing PKCβ activity in any cell or tissue in that subject.

This is in view of the lack of guidance in the specification and known unpredictability associated with predetermining the efficacy of the array of molecules, agents and chemicals claimed, and the unpredictability associated with comparing relative activities of PKCβ expression in a population and associating a risk of hypertension in that population. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and subsequent inhibition of PKCβ in an organism upon administration of any inhibitor of PKCβ and with the successful association of PKCβ activity levels in any cell or tissue in any population of individuals with their risk of having an insulin related disorder.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to methods of modulating PKCβ and eNOS in a cell or in a subject, and methods for treating any insulin related disorder, comprising

administration of any inhibitor of PKCβ. The claims are also drawn to a method of diagnosing a risk of hypertension in a subject comprising comparing the activity of PKCβ in any cell or tissue of a subject with a control.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells or tissues with a representative number of species of the broad genus comprising inhibitors of PKCβ, whereby treatment effects are provided for any insulin related disease or condition, and would require a correlation of PKCβ activity levels and the ability to predict a risk to individuals of generating any insulin related disease. Since the specification fails to provide any particular guidance for the in vivo delivery and inhibition of PKCβ in an organism using the broad genus of inhibitors claimed, and fails to provide the successful diagnosis of at risk populations for any insulin related diseases, and since determination of the factors required for such diagnoses or for in vivo success are highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 10-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Donnelly et al.

Donnelly et al (Clin. & Expl. Pharm. & Physiol., Vol. 25, pages 79-87, 1998) teach method of treating insulin related disorders in a subject comprising administration of the PKCβ inhibitor, LY333531, which inhibitor in turn modulate eNOS (see the summary and introduction on p. 79; section entitled "Protein kinase c and insulin signal transduction", pages 80-81; section entitled "Role of PKC in hyperglycaemia-induced vascular dysfunction and diabetic complications", pages 82-83; section entitled Protein kinase C inhibitors, page 85).

Claims 1-7, 10-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Ishii et al.

Ishii et al (Science, New Series, Vol. 272, No. 5262, pages 728-731, 1996) teach a method of treating insulin related disorders in a subject comprising administration of the PKCβ inhibitor, LY333531, which inhibitor in turn modulates eNOS (see the entire article, esp. the abstract, bridging paragraph pp. 728-9, last full paragraph and fig. 2 on p. 729, table 2 on p. 730, last paragraph of the article, pp. 730-1).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

(December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
5-26-06

TC1600

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PRIMARY EXAMINER